REMARKS

Status of the claims and formal matters

Claims 66-95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, 127, and 133-141 are pending in the instant application. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 were previously withdrawn from consideration. Claims 66, 67, 87-94, and 133-141 stand rejected by the Patent Office. Claims 66, 88, 89, 94, and 139 have been amended. Support for the amendment of claim 94 can be found in the last paragraph of page 19 of the specification as filed on April 21, 2006 and claim 39 as originally filed. Claim 138 has been canceled.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendment presented herein should not give rise to any estoppel.

Specification

The Examiner objects to the disclosure for certain trademark iterations. The specification has been amended as per page 2, above, to address the instant objection.

The amendments made to a paragraph on page 29 of the specification (the second paragraph shown on page 2 of this paper, above) constitute corrections of obvious typographical errors.

Double patenting

1. Claims 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 8 and 11 of copending U.S. Patent Application No. 12/027,863. Abeyance of the double patenting rejection of claims 67, 87, 88, 90, 94, 133, 134 and 136-141 is requested.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence, any statement regarding this rejection made on Applicants' behalf would be premature. Therefore, Applicants respectfully traverse this rejection and request that it be held in abeyance until subject matter is deemed allowable in this application.

2. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 25-28 of copending U.S. Patent Application No. 11/622,359. Abeyance of the double patenting rejection of claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 is requested.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence, any statement regarding this rejection made on Applicants' behalf would be premature. Therefore, Applicants respectfully traverse this rejection and request that it be held in abeyance until subject matter is deemed allowable in this application.

3. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671. Abeyance of the double patenting rejection of claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 is requested.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence, any statement regarding this rejection made on Applicants' behalf would be premature. Therefore, Applicants respectfully traverse this rejection and request that it be held in abeyance until subject matter is deemed allowable in this application.

112 Rejections

Claims 66, 67, 87-94, and 133-141 are rejected under 35 U.S.C. §112, second paragraph, for being indefinite. Specifically, the Examiner objects to the use of the phrase "less than about" in the language of the claims in question.

While Applicant disagrees with the Examiner's instant objection, in an effort to expedite the prosecution of the application, Applicant has amended the relevant claims herein by deleting the term "about" therefrom.

Consequently, Applicant requests that the instant 112 rejection be withdrawn.

103 Rejections

The Examiner has raised a number of objections under 35 U.S.C. § 103. Before addressing the instant rejections, Applicant would like to reiterate several key features of the claimed invention. The claimed invention comprises a surfactant micelle comprising a therapeutic bioactive component and a hydrophobic surfactant, with a surrounding precipitate shell comprising a polypeptide ligand and Li^+, which results in a nanocapsule of less than 50 nanometers in diameter capable of receptor-mediated targeting and uptake into the cell. As submitted previously, the claimed invention provides the first mechanically-stabilized sub-50 nm targeted particle encapsulating a therapeutic bioactive component, a particle that the prior art lacked and that provides unexpected benefits.

The ultrasmall size of the claimed composition is enabled, in part, by the formation of the core by a transiently stable hydrophobic micelle; stabilization and targeting are efficiently provided by the polypeptide shell. As likewise previously submitted, the problems that are simultaneously addressed by the claimed invention include, for example, delivery of a therapeutic agent intact into the cell, by protecting the agent from enzymatic degradation and by avoiding lysosomal degradation, in a cell-targeted manner.

A. Rejection of claims 66, 67, 87-89, 93, 94, 135, and 137-139

The Examiner has rejected claims 66, 67, 87-89, 93, 94, 135, and 137-139 under 35 U.S.C. § 103(a) as being unpatentable over Ueda, *et al.* (1997 *J Microencapsulation* 14:593-605) in view of each of Landry, *et al.* (1996 *Biomaterials* 17:715-723), Ghitescu, *et al.* (1986 *J Cell Biol* 102:1304-1311), Kondo, *et al.* (1991 *Anal Biochem* 198:3035, abst), and Boulikas (US 6,030,956). Applicant respectfully disagrees.

Lack of teaching-suggestion-motivation from the prior art.

KSR affirmed the long standing principle that a "patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 298, 418

(2007)). As discussed in the MPEP at Section 2141, the Supreme Court recognized the teaching-suggestion-motivation (TSM) test as one of a number of valid rationales that could be used to determine obviousness. *KSR International Co. v. Teleflex, Inc.,* 550 U.S. 398 (2007). Legally it is also required that in addition to a finding of TSM, there must also be a finding that there was a "reasonable expectation of success." See MPEP § 2141.02(g).

The Examiner appears to be using TSM as a basis for the rejection. Specifically, the Examiner states that the combination of the references teaches particles whose size could obviously be optimized by varying certain parameters, so that Applicant's nanoparticles would result therefrom. Applicant disagrees and submits that there must be motivation to combine the cited references in the way iterated by the Examiner, and that that motivation must either be explicit in the art or be known to the ordinary skilled person. Applicant maintains that there existed, at the time of filing, no reason why the person of ordinary skill in the art would seek, let alone reasonably expect to encounter success in such an effort, to make sub-50 nm particles, and/or particles with a shell comprising a polypeptide and Li^+, based on knowledge in the art, or based on the express teachings of the references.

Motivation. It is submitted that the Examiner has not provided the "apparent reason to combine the known elements in the way the patent claims":

> To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit." *KSR* (emphasis added).

Applicant disputes the Examiner's finding of motivation. The Examiner states that "Ueda et al., Landry et al., and Kondo et al. do not teach a particle size of 50 nm…However, they do teach that particle size can be optimized by varying parameters…". Applicant submits that the particles of the instant invention have, as one aspect, their small size. Another aspect of the inventive particles is the incorporation of the cation, Li^+, to form the precipitated shell (final paragraph of page 19, Example 1A of the specification as filed on April 21, 2006). There was no reason for skilled artisans to pursue the claimed particles with their properties such as being small and also being precipitated, based on the references' teachings, as explained further below. The Examiner has not identified any

design need or market pressure to solve a problem, whether or not disclosed by Ueda, *et al.*, that would be optimally addressed with targeted sub-50 nanometer particles, much less the targeted sub-50 nanometer, polypeptide and Li^+-bearing nanocapsules of the claimed invention. This point is explained more fully below.

Ueda

Ueda describes the preparation of loperamide hydrochloride (LPM)-loaded polylactic acid (PLA) nanoparticles employing high pressure emulsification-solvent evaporation. Ueda's nanoparticles are PLA nanoparticles containing LPM and are about 220 nm in size (particle diameter), the smallest having a diameter of about 164 nm (Table 1).

Landry

Landry describes the preparation of biodegradable poly($_{D,L}$-lactic acid)(PLA_{50}) nanoparticles coated with albumin for the purposes of understanding the mechanisms involved in their gastrointestinal degradation. Landry's nanoparticles do not contain a bioactive compound core (the PLA50 is called the core, with albumin coating it) and are found to have a 100 nm mean particle diameter.

Ghitescu

Ghitescu describes the investigation of the interaction of homologous and heterologous albumin-gold complex with capillary endothelium in the mouse lung.

Kondo

Kondo describes the establishment of a simple, rapid plasmid DNA purification method involving, in one step, the treatment of crude DNA preparations with LiCl and ethidium bromide to precipitate RNA and proteins contained in DNA preparations.

Boulikas

Boulikas describes a combination gene therapy cancer treatment involving administration of a combination of genes including wt p53, Pax5, and HSV-tk genes.

The Examiner relies on Boulikas as showing "the necessity to use gene therapy to treat diseases such as cancer", so that it would be obvious to use the particles taught by Ueda, Landry, and Kondo with a polynucleotide as bioactive agent.

The nanocapsule diameter

As mentioned above, the Examiner states that "Ueda et al., Landry et al., and Kondo et al. do not teach a particle size of 50 nm (claims 66 and 139)…It would have been obvious to one of skill in the art, at the time the invention was made, to vary the parameters in the method of optimize the size of the nanoparticles of Ueda et al., Landry et al., and Kondo et al. with the purpose of obtaining particles suitable of being delivered inside the cells via caveolae." Applicant respectfully disagrees.

Ueda, which describes an average nanoparticle size of 220 nm (and mentions nothing smaller than about 164 nm), does describe varying the nanoparticle size, but the description is more inclined to motivate the ordinarily skilled artisan to increase the nanoparticle size, rather than decrease it. In the first, Ueda states that particle size decreases with increasing PVA concentrations, but that lower concentrations of PVA are optimal (page 597, second half of first paragraph under Results and Discussion section). Of note, Table 1 on page 598 shows that even at the highest concentration of PVA listed (2.0% w/v), the particles produced still have a mean diameter of 173.9 nm. Secondly, when describing the effects of the manufacturing conditions and formulation on the size of the nanoparticles, Ueda notes that an increase in number of homogenizer cycles after 3-5 cycles does not result in a significant difference in particle size (page 597, first half of first paragraph under Results and Discussion section). Thus, the ordinarily skilled artisan would not be likely to believe that running additional homogenization cycles would lead to a decrease in particle size beyond 164 nm.

Finally, Ueda discusses the inclusion of hydrophobic surfactants to the (W/O)/W formulation, noting that the nanoparticle size consequently either increased (for sorbitan monostearate) or remained the same (for sorbitan trioleate) across a range of surfactant concentrations (pages 601 and 602). Furthermore, sorbitan monostearate, which is associated in Ueda with increasing nanoparticle size, is indicated as the most efficient surfactant (page 601, paragraph directly below Figure 3 Legend), followed by a statement that increasing sorbitan monostearate concentrations results in larger nanoparticles (page 601, second-to-last paragraph). Ueda makes no explicit statement regarding desirability of changing the size of the nanoparticles obtained through the process described therein, but those disclosures the reference does include would be likely to teach the ordinarily skilled

artisan *away from* using hydrophobic surfactants to decrease particle size, let alone to achieve nanoparticles having an average diameter of less than 50 nm.

Landry describes nanoparticles with a mean diameter of 100 nm. Landry does not provide any motivation, either explicitly or implicitly, to change that particle size. Rather, Landry is focused on the degradation of the albumin coating, as well as of the PLA_{50} core, in the gastrointestinal tract. The passages referred to by the Examiner (on page 716 of Landry) do nothing more than describe the emulsification-solvent evaporation method of preparation of nanoparticles. The reader is not left with any inclination to change the nanoparticle size.

Kondo makes no mention of any particles whatsoever.

Finally, Boulikas describes the preparation of liposomes including extrusion through membranes with a wide range of pore diameters. When describing plasmid encapsulation, Boulikas describes mixing of supercoiled plasmid DNA with small unilamellar vesicles. Unilamellar vesicles comprise one lipid bilayer, contain a large aqueous core, and are preferentially used to encapsulate water-soluble drugs. Boulikas also teaches plasmids that are encapsulated in Stealth (PEG-coated) liposomes.

The portion of Boulikas referred to by the Examiner (column 12…) provides a proposal to modify stealth liposomes with PEG, but does not teach size as an integral determinant of achieving caveolae-mediated uptake. Indeed, Boulikas' discussion of caveolae-mediated entry into cells is specific to his liposomal delivery vehicle, in contrast with the polymeric particles of Ueda and Landry. Thus, a reading of Boulikas does not leave the person of ordinary skill in the art inclined to apply its teachings to Ueda and/or Landry, let alone to decrease the latter's particle size to less than 50 nm.

With respect to liposome size, Boulikas provides no data indicating an end-product with a diameter of less than 50 nm. Rather, Boulikas limits such discussion to a broad description of liposome preparation methods that can result in a broad range of liposome sizes, and the only actual iteration of an average vesicle diameter is greater than 50 nm (60 nm, column 16, line 48) and is <u>not</u> the end-product. The person of ordinary skill in the art is, thus, left looking in the publications in the field at the time of filing for additional guidance. As previously submitted, it was known, at the time of the instant invention, that the manufacture of a liposome (such as the liposomes of Boulikas) of less than 100

nanometers was difficult to achieve due to their intrinsic instability. Kong, *et al.*, previously provided, stated that "[l]iposomes < 100 nm in diameter were not made because of instability." (Kong, *et al.* 2000 *Cancer Res* 60:4440-4445).

The Examiner's failure to provide evidence supporting the rationale for an artisan of ordinary skill to pursue the described combination is a clear error in view of the MPEP and *KSR*.

Applicant submits the rationale for creating the claimed nanocapsules are simply not taught or suggested in Ueda, *et al*. Specifically, the claimed invention is directed toward a surfactant micelle comprising a therapeutic bioactive component and a hydrophobic surfactant, surrounded by a shell comprised of a polypeptide and Li^+, which provides cell-targeted delivery and uptake via receptor mediation, in a capsule measuring less than 50 nanometers in diameter. Applicant argues that there was no motivation for the ordinary skilled person to combine the references, because the references do not motivate the ordinary skilled person to create small, targeted, drug-loaded, inventive particles based on the fact that Ueda teaches an average nanoparticle size of 220 nm (with even the smallest mean particle diameter iterated in Ueda significantly larger than Applicant's "less than 50 nm"); Landry teaches nanoparticles of a mean diameter of 100 nm and, like Ueda, provides no motivation to decrease that size; and neither Kondo nor Boulikas add, in any way relevant to the present invention, to the particle size question. These references simply do not provide the skilled person with any motivation to attempt to prepare a smaller, targeted, drug-loaded particle, with low HLB surfactants.

Therefore, the skilled person has no motivation to create the particles taught by Applicant based on the teachings of Ueda combined with Landry, Ghitescu, Kondo, and Boulikas. Reconsideration is respectfully requested.

2. *Examiner relies on impermissible hindsight to combine the elements of Ueda in the fashion of the claimed invention*

Applicant submits that the Examiner has impermissibly used the claimed invention as a guide to piece together disclosures of Ueda, Landry, Ghitescu, Kondo, and Boulikas in an effort to create a mosaic of such disclosures to argue obviousness.

The analysis supporting obviousness should be made explicit. (*KSR International Co. v. Teleflex, Inc.,* 550 U.S. 398, 418 (2007.) According to KSR, "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. See *Graham*, 383 U. S., at 36 (warning against a 'temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight' (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964.))" *KSR, 550 U.S. 398, 418 (2007.)*

The Examiner has not articulated a properly reasoned analysis, from the disclosures of the above-cited references, to support selecting and combining disparate elements of the same in the fashion of the instant invention. It is submitted that the Examiner has relied solely upon the Applicant's disclosure, and not the knowledge of an artisan of ordinary skill, to reconstruct the claimed nanocapsules.

KSR states that a reasoned analysis under Section § 103 would include identifying what would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does. Applicant maintains that the Examiner has simply generated a list of *individual elements* extracted from the cited references to match up with elements of the instant claims (for example, Ueda loperamide and surfactant micelle core and polymer shell + Landry albumin + Kondo Li^+ (where the lithium is used for an entirely distinct reason – to separate RNA and proteins from crude DNA preparations; see Section 3, below)+ Boulikas internalization aspect).

Applicant submits that the Examiner has *clearly* relied upon hindsight, and *not* the understanding of one skilled in the art at the time of the instant invention, to *selectively combine* disparate elements disclosed in the references. Examiner has not discharged the initial burden of establishing a *prima facie* case of the subject claims, and withdrawal of these objections therefore is respectfully requested.

3. *The combination of the references does not "teach" all the elements of the instant claims.*

Under MPEP 2143.03, all claim limitations must be considered. According to *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) each claim feature must be present (i.e., taught or suggested) by an asserted combination.

It is submitted that Ueda, and/or any of the other references, fails to teach not only the small size feature, but also the shell comprising a polypeptide and Li^+.

The Examiner relies on Kondo as showing that "using Li+ to precipitate proteins was routine in the prior art". Kondo precipitates RNA and proteins from DNA preparations using LiCl and ethidium bromide.

Applicant has amended claim 66 to specify that the shell comprises a polypeptide and Li^+.

Kondo describes his process of treating crude plasmid DNA preparations with lithium chloride and ethidium bromide as able to "dehydrate and deproteinize crude plasmid DNA samples, lowering the solubility of RNAs, liberating proteins, and finally precipitating all the RNA and proteins that contaminate DNA preparations…" Applicant submits that Kondo teaches the use of lithium chloride and ethidium bromide to separate DNA from protein (and RNA). Precipitation (separation) of RNA and proteins from DNA preparations would not be equated with the instant application's including Li^+ in the shell surrounding the instantly disclosed surfactant micelle.

The person of ordinary skill in the art would *not* be prompted to combine the teachings of Kondo with those of Ueda and Landry, let alone to formulate nanocapsules comprising a shell comprising polypeptide and Li^+, encapsulating a bioactive agent such as a polynucleotide.

4. *Long felt need.*

According to MPEP 2141, secondary considerations may rebut any *prima facie* case of obviousness. One such secondary consideration is whether "the claimed invention [satisfies] a long-felt need which was recognized, persistent and not solved by others." Specifically, as reiterated by the Supreme Court in KSR, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. Objective evidence relevant to the issue of obviousness must

be evaluated by Office personnel. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results.

At the time the instant invention was made, there had been, for at least ten years, a need in the field of drug delivery to combine cell-targeting and efficient, non-degradative uptake. The emerging view was that any solution was likely to be more complex than originally believed (i.e., unpredictable, with no reasonable expectation of success). Applicant's nanocapsule system addresses this long-felt need, producing cell-targeted, stabilized nanocapsules of sub-50 nm size that avoid substantial lysosomal accumulation and degradation, providing uniform, intact delivery of a therapeutic agent.

Heidel, *et al.* summarized the views held by many for years, *i.e.*, that addressing the challenges of drug delivery isn't simply a matter of identifying useful ingredients or adding components to known vesicle structures; "the challenges of creating a nonviral delivery system are many[, but] we believe that one of the most daunting….is the integration of the components into a workable system that combines the attributes of the components without suffering losses because of their integration."[1]

Accordingly, it is submitted that the claimed nanocapsules meet significant, long-felt needs and are a significant leap over the teachings of the prior art. It is, therefore, respectfully submitted that Applicant's demonstration of meeting a long-felt need is further evidence of non-obviousness, and it is requested that this evidence be considered by the Examiner.

B. ***Rejection of claims 66, 67, 87-90, 93, 94, 135, and 136-139***

The Examiner has rejected claims 66, 67, 87-90, 93, 94, 135, and 136-139 under 35 U.S.C. § 103(a) as being unpatentable over Ueda, *et al.* (1997 *J Microencapsulation* 14:593-605) in view of each of Landry, *et al.* (1996 *Biomaterials* 17:715-723), Ghitescu, *et al.* (1986 *J Cell Biol* 102:1304-1311), Kondo, *et al.* (1991 *Anal Biochem* 198:3035, abst), and Boulikas (US 6,030,956), in further view of Krishnan, *et al.* (1999 *Colloids Surfaces A: Physicochem. Eng. Aspects* 149:355-366). Applicant respectfully disagrees.

[1] J. Heidel et al., "Molecular Conjugates", *Adv. Biochem. Engin./Biotechnol*: 99, 7-39 (2005). Copy provided in IDS accompanying this response.

Ueda, Landry, Ghitescu, Kondo, and Boulikas are addressed in Section A, above, including, in particular, Ueda's teaching that the use of hydrophobic surfactants can increase nanoparticle size, and certainly won't decrease it. Applicant would, however, like to address the Examiner's statement that "Ueda et al. teach that surfactants that an HLB less than 5.0 is necessary for efficient incorporation of hydrophilic therapeutic agents…" Ueda investigates the optimization of the preparation of LPM-loaded PLA nanoparticles. LPM, or loperamide hydrochloride, is a lipophilic therapeutic agent, not a hydrophilic one, "because water-soluble drugs easily partition into the aqueous phase from the organic phase during emulsification, evaporation, as well as purification" (page 597, 3rd paragraph).

Krishnan

Krishnan investigates the effect of interactions between acetylenic diol surfactants and some polymers used in the graphic arts industry on the dynamic surface tension of such polymer/surfactant mixtures. The entire study is carried out within the context of water-based printing inks. In other words, Krishnan's investigation is an entirely unrelated field from that of the instant invention, as well as from that of the other references cited.

Furthermore, Krishnan's comparison of the surfactant Surfynol 104H (75% solution of 2, 4, 7, 9-tetramethyl-5-decyne-4, 7-diol in ethylene glycol) with the surfactant Surfynol 440 revealed a lower dynamic surface tension (DST) for 440, stronger polymer/surfactant interactions, teaching the ordinarily skilled artisan the superiority of the 440 surfactant – the surfactant with a noted HLB of 8 – over the 104 surfactant in the context of polymer/surfactant interaction. Thus, the person of ordinary skill in the art would be inclined to use the Surfynol 440 surfactant, rather than the Surfynol 104H, in the Examiner-cited context.

Finally, Krishnan fails to cure the defects of the combination of the references discussed in Section A, for example, it does not assist the ordinarily skilled artisan in achieving nanocapsule of less than 50 nm diameter.

C. ***Rejection of claims 66, 67, 87-89, 91-94, 135, and 137-139***

The Examiner has rejected claims 66, 67, 87-89, 91-94, 135, and 137-139 under 35 U.S.C. § 103(a) as being unpatentable over Iwata, *et al.* (1992 *J Microencapsulation* 9:201-214) in view of each of Davies, *et al.* (1987 *J Colloid and Interface Sci* 116:88-99, abst),

Levy, *et al.* (WO96/20698), Chang, *et al.* (1996 *J Pharmaceutical Sci* 85:13225-13230), and Kondo, *et al.* (1991 *Anal Biochem* 198:3035, abst). Applicant respectfully disagrees.

Iwata

Iwata describes the preparation of multi-phase microspheres containing several W/O emulsion droplets via multiple emulsion solvent evaporation using water-soluble model drugs. Microspheres generally range in diameter from 1 μm to 1000 μm, and those shown in Figures 3 and 7 of Iwata certainly appear to be upwards of 20 μm – far greater than the less than 50 nm diameter of the nanocapsules disclosed in the instant application.

In addition, Iwata makes no mention of a polypeptide-comprising shell such as that included in the pending claim language.

Davies

Davies is an abstract relied upon by the Examiner for its iteration that Span80 (sorbitan monooleate) has an HLB value of 4.3. Beyond that, Davies is limited to a comparison in W/O emulsion generation between the combination of water with Span80 and that of water with Span80 with Tween80. The reference is silent on a core of bioactive component, as it is on a shell.

Levy

The Examiner relies on Levy to provide the ordinarily skilled artisan having read Iwata with the motivation i) to coat its microparticles with a polypeptide capable of binding a cell-surface receptor, ii) to manipulate the conditions of the solvent-evaporation technique to get nanoparticles of 20-35 nm size, and iii) to use nanoparticles in gene therapy. Applicant respectfully disagrees.

In the first, Iwata is focused on improving drug loading (into microsphere) efficiencies of water-soluble compounds. Iwata neither discusses nor implies adding a targeting element to the microspheres. Thus, the ordinarily skilled artisan is not motivated by Iwata to consider the incorporation of such an element. *Were* the artisan thus inclined, he would certainly focus on the significant bulk of microsphere literature available, rather than a publication focused on nanoparticles. Levy discloses *nanoparticles* comprising a biocompatible, biodegradable polymer core having an average diameter of typically less than 300 nm and having at least one bioactive agent &/or surface modifying agent associated or incorporated therewith.

Likewise, Iwata does not provide any motivation to develop nanoparticles. Rather, Iwata focuses entirely on microspheres containing several water-in-oil emulsion droplets. Iwata reports the promise of its multi-phase microspheres of PLA and PLGA for improved drug-loading efficiency of water-soluble compounds. Any attempt on Iwata's part to decrease the size of the microspheres would be made while maintaining that drug-loading level, and there is no indication that such an attempt would lead to leaving microspheres containing multiple W/O emulsion droplets altogether and preparing nanoparticles instead.

Applicant suggests that, while the pending claims are composition claims, these compositions are critically affected by the method of preparation employed to synthesize them. Iwata disperses an aqueous solution of drug, gelatin, hydrophilic surfactant, and water in an organic solution of soybean oil and a blend of hydrophobic surfactants to create a W/O emulsion, which is then dispersed into a solution of PLA or PLGA polymer and polar acetonitrile solvent to create a W/O/W emulsion, which, upon solvent evaporation, produces microspheres measuring approximately 200 microns in diameter, and each encapsulating a plurality of emulsion droplets (see, for example, Figures 1, 7, and 8). In contrast, Levy, prior to addition of surface-modified agents, disperses an aqueous solution of drug and water into an organic solution of polymer such as PLGA and a hydrophilic surfactant, to form a W/O emulsion, which is then dispersed into a solution of water and hydrophilic emulsifier (e.g., polyvinyl alcohol, PVA) to create a (W/O)/W emulsion, which, upon solvent evaporation, produces nanoparticles measuring approximately 100+ nm in diameter, and each encapsulating a single emulsion droplet.

Iwata's and Levy's processes and end-products are significantly different – for example, they differ in the use of hydrophobic vs. hydrophilic surfactants, in size, and in encapsulation of multiple vs. single droplets. Rather than considering whether or not Iwata's process for preparation of microsphere is <u>suitable</u> for modification by Levy's process for preparing nanoparticles, which Applicant submits cannot reasonably be expected to be the case, the Examiner has simply combined elements from the two references' processes to arrive at the instant invention. This certainly qualifies as impermissible hindsight.

It was, in fact, well established, at the time of the invention, that "the problems associated with multiple emulsions (either (W/O)/W or (O/W)/W) are numerous and

remain mostly unsolved" (Ficheux, *et al.* 1998 *Langmuir* 14:2702-2706, submitted herewith). In view of the well-known challenges of emulsion formulations, the person of ordinary skill in the art would not reasonably expect that the elements of the Iwata and Levy preparation processes would be directly interchangeable.

Even if the ordinarily skilled artisan were inclined to apply the teachings of Levy to modify the teachings of Iwata, as described above, the result would fail to teach a shell comprising a polypeptide *and* Li^+.

To that end, the Examiner states that precipitating the polypeptide coat with a cationic precipitating agent such as Li^+ was suggested by the prior art. In the first, the Examiner points to Chang.

Chang

Chang describes an investigation of freezing-induced denaturation of proteins that can occur in the development of protein pharmaceuticals and result, for example, from prolonged storing in a frozen state. The invention at hand is entirely different. Chang is likely to offer little more than the desire to avoid freeze-drying polypeptide coatings based on concern regarding consequent denaturation of the polypeptide.

The Examiner also refers to Kondo to show that precipitating the polypeptide coat with a cationic precipitating agent such as Li^+ was suggested by the prior art.

Kondo

As iterated above, Kondo's lithium cation is provided in the form of LiCl with ethidium bromide in a process to purify DNA plasmid from cellular RNA and protein. The claimed invention does not teach the use of lithium to remove RNA and protein from DNA. Rather, the claimed invention teaches the inclusion of lithium to stabilize nanocapsules comprising for example DNA cargo *and* a polypeptide shell.

With regard to the Examiner's statement that "the conditions of the solvent-evaporation technique…of Levy…could be manipulated to obtain nanoparticles with a size of 20-35 nm…", Applicant points out that Levy's nanoparticles in question are described in Example 6 as "ultrasmall nanoparticles" and are the result of a very specific co-solvent technique employed by Levy. Furthermore, these ultrasmall nanoparticles do not include a shell comprising a polypeptide and Li^+.

None of the formulations actually prepared and characterized in Levy's examples has an average particle diameter of less than 50 nm. For example, those particles prepared and described in Levy for intravascular administration (the Examiner points to Levy's particles suitable for intravascular administration in the Office Action) have an average particle size of "145.4 ± 44.1 nm" (Example 20).

Of additional note with respect to particle size and the Examiner's attempt to combine the teachings of Iwata with those of Levy to achieve a smaller microsphere size, Ueda states that, while the use of (W/O)/W solvent evaporation method has been employed for successful entrapment of drug in microspheres, it "seems not to be feasible for the preparation of nanoparticles in view of the particle size requirement." (page 594, 4th paragraph).

With regard to the "conditions of the solvent-evaporation technique…of Levy" that the Examiner purports can be manipulated to obtain nanoparticles of a size of 20-35 nm, Applicant notes that one of the conditions cited is the use of "certain emulsifying agents". The agents in question, according to Example 6 (wherein the "ultrasmall nanoparticles" are mentioned), are DMAB, CTAB, and CTAC. All three agents are hydrophilic agents and have HLB values of 10 or higher. Thus, Levy's "ultrasmall nanoparticles" result from the use of hydrophilic surfactants. In marked contrast, the instant invention as claimed includes a surfactant having an HLB value of less than 6, i.e., a hydrophobic surfactant. A person of ordinary skill in the art's reading of Levy would, thus, certainly not motivate them to consider utilizing a surfactant with an HLB value of less than 6 to prepare nanocapsules with an average diameter of less than 50 nm.

Finally, the Examiner states that the bioactive component being a polynucleotide is obvious, because Levy teaches using nanoparticles in gene therapy. Again, Applicant must note that the person of ordinary skill in the art is unlikely to reasonably expect that a nanoparticle can be substituted for Iwata's microspheres. Iwata focuses on water-soluble drugs, including biological response modifiers. Iwata makes no mention whatsoever of using microspheres for delivery of polynucleotides in gene therapy, let alone substituting the microspheres for nanoparticles. It would appear that the Examiner is using impermissible hindsight to arrive at the claimed invention.

D. ***Rejection of claims 66, 67, 87-89, 91-94, 135, and 137-139***

The Examiner has rejected claims 66, 67, 87-89, 91-94, 135, and 137-139 under 35 U.S.C. § 103(a) as being unpatentable over Iwata, *et al.* (1992 *J Microencapsulation* 9:201-214) in view of each of Davies, *et al.* (1987 *J Colloid and Interface Sci* 116:88-99, abst), Levy, *et al.* (WO96/20698), Chang, *et al.* (1996 *J Pharmaceutical Sci* 85:13225-13230), and Kondo, *et al.* (1991 *Anal Biochem* 198:3035, abst), in further view of Schneider, *et al.* (1998 *FEBS Letters* 429:269-273). Applicant respectfully disagrees.

Iwata, Davies, Levy, Chang, and Kondo are discussed in Section C, above.

Schneider

Schneider describes an effort to improve the targeting of a non-viral integrin-mediated gene transfer system to airway epithelia by synthesizing two peptides comprising receptor-targeting domain and DNA-binding moiety.

The Examiner states that "It would have been obvious to one of skill in the art, at the time the invention was made to modify the nanoparticles of Iwata et al., Davies et al., Levy et al. Chang et al., and Kondo et al. by coating them with tenascin with the intent to target the particles to $\alpha_9\beta_1$ integrin-expressing cells, with a reasonable expectation of success. The motivation to do so is provided by Schneider et al., who teach that using ligands for $\alpha_9\beta_1$ integrin is promising for the development of targeted gene therapy..."

Applicant respectfully disagrees with this interpretation of Schneider. Schneider provides a more basic study of an extended peptide, which may be useful in the development of gene therapy vectors or drugs targeting certain integrins. Applicant reminds the Examiner of the previously cited later Schneider reference (1999 FEBS Letters 458:329-332), wherein Schneider found that when polypeptide-DNA complexes were associated with a delivery vehicle (LipofectAMINE ^{TM}), targeting specificity was *reduced.* This led to the conclusion that "in the presence of the LipofectAMINE ^{TM} internalization of the complex occurs to a large extent by an integrin-independent mechanism." This leaves the person of ordinary skill in the art with an understanding that the polypeptide in question was not effective in targeted gene delivery when associated with a delivery vehicle (such as, for example, a nanocapsule according to the invention). Not only does Schneider provide another example of the significant challenges of integrating components into a viable drug delivery system, but it teaches away from the instant invention. "A reference

may be said to teach away when a person of ordinary skill, upon reading the reference,…would be led in a direction divergent from the path that was taken by the applicant." (*Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999)).

Accordingly, based on objective evidence, there was, at the time of the instant invention, no "expectation of success" for stable sub-50 nm nanocapsules with cell-targeting and uptake capabilities. The cited references provide no parameters or results to suggest otherwise. Thus, the Examiner must conclude that there was no expectation of success for the instant invention.

CONCLUSION

For the reasons set forth above, Applicant respectfully submits that the claims as filed and as presented herewith are allowable over the art of record, and reconsideration and issuance of a Notice of Allowance are respectfully requested. Should it be considered helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for a two-month extension of time pursuant to 37 C.F.R. § 1.136(a) and an authorization to charge all fees therefor to deposit account No. 19-5117. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

Date: December 22, 2010 /Marina Heusch/

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